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Associations between residual disease and survival in epithelial ovarian cancer by histologic type

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HIGHLIGHTS

- Cytoreduction to no visible disease predicts survival in serous, mucinous and clear cell ovarian cancer.
- Prognostic significance of residual disease does not differ by histologic type.
- Association of residual disease and survival is independent of chemoresponsiveness.

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ABSTRACT

Objective. Surgical cytoreduction has been postulated to affect survival by increasing the efficacy of chemotherapy in ovarian cancer. We hypothesized that women with high-grade serous ovarian cancer, which usually responds to chemotherapy, would derive greater benefit from complete cytoreduction than those with histologic subtypes that are less responsive to chemotherapy, such as mucinous and clear cell carcinoma.

Methods. We conducted a retrospective cohort study of patients who underwent primary cytoreductive surgery and adjuvant chemotherapy for stage IIIC or IV epithelial ovarian cancer from 2011 to 2013 using data from the National Cancer Database. We constructed multivariable models to quantify the magnitude of associations between residual disease status (no residual disease, ≤1 cm, or >1 cm) and all-cause mortality by histologic type among women with clear cell, mucinous, and high-grade serous ovarian cancer. Because 26% of the sample had unknown residual disease status, we used multiple imputations in the primary analysis.

Results. We identified 6,013 women with stage IIIC and IV high-grade serous, 307 with clear cell, and 140 with mucinous histology. The association between residual disease status and mortality hazard did not differ significantly among histologic subtypes of ovarian cancer (p for interaction = 0.32). In covariate adjusted models, compared to suboptimal cytoreduction, cytoreduction to no gross disease was associated with a hazard reduction of 42% in high-grade serous carcinoma (hazard ratio [HR] = 0.58, 95% confidence interval [CI] = 0.49–0.68), 61% in clear cell carcinoma (HR = 0.39, 95% CI = 0.22–0.69), and 54% in mucinous carcinoma (HR = 0.46, 95% CI = 0.22–0.99).

Conclusions. We found no evidence that surgical cytoreduction was of greater prognostic importance in high-grade serous carcinomas than in histologies that are less responsive to chemotherapy.

1. Introduction

Epithelial ovarian cancer is usually diagnosed after it has metastasized within the peritoneal cavity [1]. In such cases, treatment consists of surgery to remove all visible cancer in combination with chemotherapy [2]. Residual disease after cytoreductive surgery is a strong predictor of survival [3–9]. The association between residual disease and survival has been postulated to be causal, leading many centers to adopt increasingly aggressive surgical maneuvers aimed at resection of all visible disease prior to administration of chemotherapy [10–13]. While two randomized studies have found that neoadjuvant chemotherapy is non-inferior to primary cytoreductive surgery for women with IIIC and IV epithelial ovarian cancer, national guidelines continue to recommend primary surgery for patients with resectable disease who are fit for surgery [14].

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While the association between residual tumor and survival in epithelial ovarian cancer is beyond dispute, few studies have empirically evaluated the nature of this relationship. It has been proposed that cytoreduction improves the efficacy of chemotherapy by way of mechanisms which assume that ovarian cancer cells are innately sensitive to chemotherapy, including: 1) resection of poorly vascularized areas of tumors removes pharmacologic sanctuaries, leading to improved drug penetration; 2) cytoreduction removes tumor cells in the plateau phase of cell growth, which are less chemosensitive; 3) resection of all macroscopic disease removes chemoresistant clones; 4) smaller tumors respond to fewer cycles of chemotherapy, thereby decreasing their likelihood of acquiring chemoresistance [15–20].

Although generally considered to be a chemosensitive disease, some subtypes of epithelial ovarian cancer respond poorly to chemotherapy. Women diagnosed with serous ovarian cancer typically respond to platinum-based chemotherapy regimens (response rate, 64.9–81.0%), but the response rates are lower among women with mucinous (12.5–38.5%) and clear cell ovarian cancer (11.1–45%) [21–25]. Despite these differences in chemoresponsiveness, debulking to minimal or no residual disease remains the standard of care for all histologic subtypes.

If the association between residual disease and survival is the result of mechanisms that depend on the innate chemoresponsiveness of epithelial ovarian cancer, we expect the magnitude of the survival benefit associated with complete cytoreduction to differ among histologic types. Specifically, if the efficacy of cytoreduction depends on the tumor's likelihood to respond to chemotherapy, then the survival benefit associated with complete cytoreduction will be greater in women with high-grade serous ovarian cancer compared with ovarian clear cell and mucinous carcinoma. To test this prediction, we undertook a retrospective cohort study comparing the prognostic significance of residual status by histologic subtype, using data from a national cancer registry.

2. Methods

This study used data from the National Cancer Database (NCDB), a collaboration of the American College of Surgeons and the American Cancer Society, which aggregates data from the cancer registries of >1500 Commission on Cancer–accredited hospitals in the United States. The data are abstracted by trained cancer registrars in each institution and represent >70% of new cancer diagnoses nationwide [26]. This study was exempted from Institutional Review Board oversight by the Partners Healthcare Research Committee.

We identified all subjects in the NCDB participant user file who were diagnosed with stage IIIC and IV epithelial ovarian cancer from 2011 to 2013. Since 2010, the Commission on Cancer has required cancer registrars to abstract residual tumor status from the medical record of all ovarian cancer patients, based on surgeon report [27]. We excluded the first year that residual disease status data was available to allow for implementation of this new practice. Patients diagnosed after 2013 were not included because no survival information is available for these patients. We excluded women who received no treatment, received chemotherapy prior to surgery, did not receive adjuvant chemotherapy after surgery, and those with unknown treatment (Fig. 1). We also excluded patients with histologic subtypes of epithelial ovarian cancer other than clear cell, mucinous and high-serous carcinoma, as well as those who were not treated at the reporting facility, lacked pathological confirmation, had concurrent or prior malignancy or lacked survival data (Fig. 1).

The main exposure of interest was residual disease status, which was classified as no residual disease (R_0), optimal cytoreduction (residual disease measuring 1 cm or less), and suboptimal cytoreduction (residual disease measuring >1 cm). The primary outcome was time from diagnosis to death from any cause, or to last contact, as recorded by the cancer registrar. Unless otherwise stated all analyses were stratified by histologic subtype, defined as clear cell carcinoma, mucinous carcinoma, or high-grade serous carcinoma.

We categorized age at diagnosis as <40, 40–49, 50–59, 60–69, 70–79, or 80 years and over. Stage was defined as American Joint Committee on Cancer (AJCC) pathological stage, or when AJCC pathological stage was missing, as AJCC clinical stage. We categorized race/ethnicity as Asian, black, Hispanic, white, or other/unknown. Geographic region was based on treating facility and was categorized per United States Census Region (Midwest, Northeast, South, and West). We classified subjects as having or lacking medical comorbidities using the Deyo adaptation of the Charlson Comorbidity Index [28]. Facility types were categorized as academic, non-academic, or other/unknown. We calculated mean number of cases of advanced ovarian cancer treated in each reporting hospital and categorized hospitals into quartiles of volume (<9, 9–16, 17–26, 27 or more cases per year).

Noting a relatively high proportion of cases with unknown residual disease status in the study population (26%), we compared distributions of covariates and all-cause mortality between women with known and unknown residual disease status (Supplementary Table 1). After determining that residual disease status was unlikely to be missing completely at random, we used chained equations to impute residual disease status in 25 datasets that were used in the primary multiple imputations analysis [29]. As a secondary analysis we performed a complete case-case analysis that included only the 74% of patients with known residual disease status.

We performed sensitivity analyses assessing whether deviations from the missing-at-random assumption, inherent to the validity of multiple imputations, could alter the study's main result. Since patients with missing data had higher mortality than those with known residual disease status, we focused on the possibility that missing residual disease status was associated with suboptimal cytoreduction to a greater degree than predicted by the imputation model. To evaluate impact of higher than predicted suboptimal debulking rates among women with unknown residual disease status, we repeated the main analysis in a dataset where all women with missing residual disease were categorized as having had a suboptimal cytoreduction. In a second set of sensitivity analyses, we considered the possibility that there was an unmeasured association between histologic subtype and unrecorded suboptimal cytoreduction. To test the impact of such an association, we created three modified datasets in which the proportion of patients with imputed suboptimal debulking was doubled among women with only one histologic subtype, and repeated the main analysis in each of these datasets.

We compared the distributions of demographic, histopathologic, and treatment variables by histologic subtype using the Pearson χ^2 test. We plotted survival functions, stratified by residual disease status for subjects with each histologic subtype, using the Kaplan–Meier method. We tested whether unadjusted overall survival differed by residual status using the Wald test in a univariable Cox models. We also created corresponding covariate-adjusted survival curves using a flexible parametric survival model to predict expected survival probabilities for subjects with each residual disease status and histology, but with otherwise identical covariate distributions in terms of age group, stage, race/ethnicity, insurance status, facility type, hospital annual ovarian cancer volume, and presence of comorbidities [30]. Survival probabilities were predicted for each imputed data set and averaged. We selected covariates a priori based on their known association with all-cause mortality in ovarian cancer [31,32].

To determine whether the magnitude of association between residual disease status and survival differed among histologic subtypes, we used a Wald test to assess whether an interaction between histologic subtype and residual disease status was statistically significant in a multivariable Cox proportional hazard model. We quantified the magnitude of associations between residual status and all-cause mortality using crude and adjusted hazard ratios (HR) obtained from univariable and multivariable Cox proportional hazards models. Multivariable models

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